

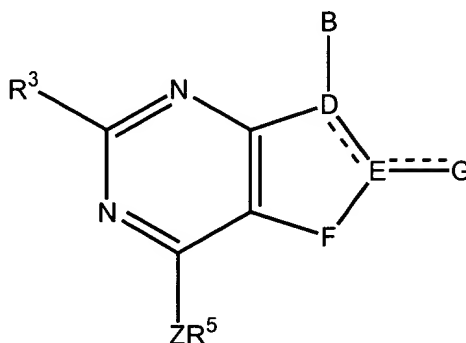
application. An final rejection issued on June 27, 2001. The present response is submitted within one year of the period set for response to thereto.

Please amend the application as follows:

IN THE CLAIMS

Amend claims 18 and 25 to read as follows:

18. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4 ; provided that either 1) exactly one of D or E is nitrogen and F is CHR^4 or 2) F is NR^4 and neither D nor E is nitrogen;

G, when single bonded to E is hydrogen, C_1 - C_4 alkyl, $-S(C_1-C_4 \text{ alkyl})$, $-O(C_1-C_4 \text{ alkyl})$, NH_2 , $-NH(C_1-C_4 \text{ alkyl})$ or $-N(C_1-C_2 \text{ alkyl})(C_1-C_4 \text{ alkyl})$ wherein each of the C_1 - C_4 alkyl groups of G may optionally be substituted by one hydroxy, $-O(C_1-C_2 \text{ alkyl})$ or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, C_1 - C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, CF_3 , $-C(=O)O-(C_1-C_4)alkyl$, $-OC(=O)(C_1-C_4)alkyl$, $OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl)$, $-NHCO(C_1-C_4 alkyl)$, $-COOH$, $-COO(C_1-C_4 alkyl)$, $-CONH(C_1-C_4 alkyl)$, $-CON(C_1-C_4 alkyl)(C_1-C_2 alkyl)$, $-S(C_1-C_4 alkyl)$, $-CN$, NO_2 , $-SO(C_1-C_4 alkyl)$, $-SO_2(C_1-C_4 alkyl)$, $-SO_2NH(C_1-C_4 alkyl)$, $SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl)$, wherein a carbon-carbon single bond of each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1 - C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R^2 is aryl or $(C_1-C_4 alkylene)aryl$, wherein said aryl and the aryl moiety of said $(C_1-C_4 alkylene)aryl$ is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3 - C_8 cycloalkyl or $(C_1-C_6 alkylene)(C_3-C_8 cycloalkyl)$, wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said $(C_1-C_6 alkylene)(C_3-C_8 cycloalkyl)$ may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1 - C_4 alkyl, benzyl and C_1 - C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, $-OC(=O)(C_1-C_6 alkyl)$, $OC(=O)N(C_1-C_4 alkyl)(C_1-C_2 alkyl)$, $-S(C_1-C_6 alkyl)$, amino, $-NH(C_1-C_2 alkyl)$, $-N(C_1-C_2 alkyl)(C_1-C_4 alkyl)$, $-N(C_1-C_4 alkyl)-CO-(C_1-C_4 alkyl)$, $-NHCO(C_1-C_4 alkyl)$, $-COOH$, $-COO(C_1-C_4 alkyl)$, $-CONH(C_1-C_4 alkyl)$, $CON(C_1-C_4 alkyl)(C_1-C_2 alkyl)$, $-SH$, $-CN$, $-NO_2$, $-SO(C_1-C_4 alkyl)$, $-SO_2(C_1-C_4 alkyl)$, $-SO_2NH(C_1-C_4 alkyl)$ and $-SO_2N(C_1-C_4 alkyl)(C_1-C_2 alkyl)$;

$-NR^1R^2$ or $-CR^1R^2R^{10}$ may form a 3 to 8 membered ring, that in the case of $-CR^1R^2R^{10}$ is carbocyclic, said ring consisting of single bonds, wherein, when said ring has from 5 to 8 members, one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and

independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1 - C_4 alkyl, benzyl and C_1 - C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R^3 is hydrogen, C_1 - C_4 alkyl, $O(C_1$ - C_4 alkyl), chloro, fluoro, bromo, iodo, $-CN$, $-S(C_1$ - C_4 alkyl) or $-SO_2(C_1$ - C_4 alkyl) wherein each of the $(C_1$ - C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and $(C_1$ - C_2 alkoxy);

each of R^4 is, independently hydrogen, $(C_1$ - C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, $-O(C_1$ - C_4 alkyl), $N(C_1$ - C_4 alkyl) $(C_1$ - C_2 alkyl), $-S(C_1$ - C_4 alkyl), $-SO(C_1$ - C_4 alkyl), $-SO_2(C_1$ - C_4 alkyl), $-CO(C_1$ - C_4 alkyl), $-C(=O)H$ or $C(=O)O(C_1$ - C_4 alkyl), wherein one or two of the carbon-carbon single bonds in each of the $(C_1$ - C_6 alkyl) and $(C_1$ - C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said $(C_1$ - C_6 alkyl) and $(C_1$ - C_4 alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1 - C_3 alkoxy, dimethylamino, methylamino, ethylamino, $-NHC(=O)CH_3$, fluoro, chloro, $-CN$, $-COOH$, $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl) and NO_2 ;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3 - C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein N^4 is hydrogen, C_1 - C_4 is alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C_1 - C_6 alkyl and $-O(C_1$ - C_6 alkyl) and one of said substituents may be selected from bromo, iodo, formyl, $-CN$, $-CF_3$, $-NO_2$, $-NH_2$, $-NH(C_1$ - C_4 alkyl), $-N(C_1$ - C_2 alkyl) $(C_1$ - C_6 alkyl), $-C(=O)O(C_1$ - C_4 alkyl), $-C(=O)(C_1$ - C_4 alkyl), $-COOH$, $-SO_2NH(C_1$ - C_4 alkyl), $-SO_2N(C_1$ - C_2 alkyl) $(C_1$ - C_4 alkyl), $-SO_2NH_2$, $NHSO_2(C_1$ - C_4 alkyl), $-S(C_1$ - C_6

alkyl) and $\text{-SO}_2(\text{C}_1\text{-C}_6 \text{ alkyl})$, and wherein each of the $\text{C}_1\text{-C}_4$ alkyl and $\text{C}_1\text{-C}_6$ alkyl, moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl; and furthermore wherein when R^5 is phenyl or pyridyl substituted with three substituents; said substituents can further be selected from $(\text{C}_1\text{-C}_4 \text{ alkyl})\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, OCF_3 , and fluoro, and one carbon-carbon single bond of each $(\text{C}_1\text{-C}_4)$ alkyl group of said substituents having between two and four carbon atoms may be optionally replaced with a carbon-carbon double or triple bond; or R^5 is pyrimidyl substituted by three substituents independently selected from $\text{C}_1\text{-C}_4$ alkyl, $\text{-O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, CF_3 , OCF_3 , -CHO , $(\text{C}_1\text{-C}_4 \text{ alkyl})\text{-OH}$, CN , Cl , F , Br , I and NO_2 , wherein a carbon-carbon single bond of said $(\text{C}_1\text{-C}_4)$ alkyl groups having been two and four carbon atoms may optionally be replaced by a carbon-carbon double or triple bond;

R^7 is hydrogen, $\text{C}_1\text{-C}_4$ alkyl, halo, cyano, hydroxy, $\text{-O}(\text{C}_1\text{-C}_4 \text{ alkyl})$ $\text{-C(=O)}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $\text{-C(=O)O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, -OCF_3 , -CF_3 , $\text{-CH}_2\text{-OH}$, $\text{-CH}_2\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$;

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

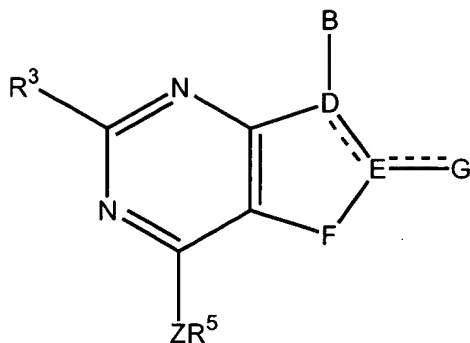
R^{11} is hydrogen or $\text{C}_1\text{-C}_4$ alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b) one of E, D and F must be nitrogen or substituted nitrogen, and only one of E, D and F can be nitrogen or substituted nitrogen;

Z is NH , oxygen, sulfur, $\text{-N}(\text{C}_1\text{-C}_4 \text{ alkyl})$, $\text{-NC(=O)}(\text{C}_1\text{-C}_2 \text{ alkyl})$ $\text{NC(-O)O}(\text{C}_1\text{-C}_2 \text{ alkyl})$ or $\text{CR}^{13} \text{R}^{14}$ wherein R^{13} and R^{14} are independently selected from hydrogen, trifluoromethyl and methyl with the exception that one of R^{13} and R^{14} can be cyano;

or a pharmaceutically acceptable salt of such compound.

25. A compound of the formula



wherein the dashed lines represent optional double bonds;

B is $-NR^1R^2$, $-CR^1R^2R^{10}$, $-C(=CR^2R^{11})R^1$, $-NHCR^1R^2R^{10}$, $-OCR^1R^2R^{10}$, $-SCR^1R^2R^{10}$, $CR^2R^{10}NHR^1$, $-CR^2R^{10}OR^1$, $-CR^2R^{10}SR^1$ or $-COR^2$;

E is nitrogen, CH or carbon;

D is nitrogen and is single bonded to all atoms to which it is attached, or D is carbon and is double bonded to E, or D is CH and is single bonded to E;

F is CHR^4 or NR^4 ; provided that either 1) exactly one of D or E is nitrogen and F is CHR^4 or 2) F is NR^4 and neither D nor E is nitrogen;

G, when single bonded to E is hydrogen, C_1 - C_4 alkyl, $-S(C_1$ - C_4 alkyl), $-O(C_1$ - C_4 alkyl), NH_2 , $-NH(C_1$ - C_4 alkyl) or $-N(C_1$ - C_2 alkyl)(C_1 - C_4 alkyl) wherein each of the C_1 - C_4 alkyl groups of G may optionally be substituted by one hydroxy, $-O(C_1$ - C_2 alkyl) or fluoro group; and G when double bonded to E is oxygen, sulfur or NH; and G, when E is nitrogen and double bonded to D, is absent;

R^1 is hydrogen, C_1 - C_6 alkyl optionally substituted with one or two substituents R^8 independently selected from hydroxy, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, CF_3 , $-C(=O)O(C_1$ - C_4)alkyl, $-OC(=O)(C_1$ - C_4)alkyl, $OC(=O)N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), $-NHCO(C_1$ - C_4 alkyl), $-COOH$, $-COO(C_1$ - C_4 alkyl), $-CONH(C_1$ - C_4 alkyl), $-CON(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), $-S(C_1$ - C_4 alkyl), $-CN$, NO_2 , $-SO(C_1$ - C_4 alkyl), $-SO_2(C_1$ - C_4 alkyl), $-SO_2NH(C_1$ - C_4 alkyl), $SO_2N(C_1$ - C_4 alkyl)(C_1 - C_2 alkyl), wherein a carbon-carbon single bond of each of the C_1 - C_4 alkyl groups in the foregoing R^1 groups having at least two carbons may optionally be replaced with a carbon-carbon double or triple bond, and one or two carbon-carbon single bonds of each of the C_1 - C_4 alkyl groups in the

foregoing R^1 groups having four carbon atoms may optionally be replaced with a carbon-carbon double or triple bond; R^2 is C_1 - C_{12} alkyl wherein one carbon-carbon single bond of any said alkyl group having at least two carbons, one or two carbon-carbon single bonds of any alkyl having at least four carbons, and from one to three carbon-carbon single bonds of any said alkyl having at least six carbons may optionally be replaced with a carbon-carbon double or triple bond; or R^2 is aryl or (C_1 - C_4 alkylene)aryl, wherein said aryl and the aryl moiety of said (C_1 - C_4 alkylene)aryl is selected from phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidinyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, pyrazolyl, pyrrolyl, indolyl, pyrrolopyridyl, oxazolyl and benzoxazolyl; or R^2 is C_3 - C_8 cycloalkyl or (C_1 - C_6 alkylene)(C_3 - C_8 cycloalkyl), wherein one or two of the carbon atoms of said cycloalkyl and the 5 to 8 membered cycloalkyl moieties of said (C_1 - C_6 alkylene)(C_3 - C_8 cycloalkyl) may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^2 wherein Z^2 is selected from hydrogen, C_1 - C_4 alkyl, benzyl and C_1 - C_4 alkanoyl, and wherein each of the foregoing R^2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, hydroxy and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, $-OC(=O)(C_1-C_6$ alkyl), $OC(=O)N(C_1-C_4$ alkyl)(C_1-C_2 alkyl), $-S(C_1-C_6$ alkyl), amino, $-NH(C_1-C_2$ alkyl), $-N(C_1-C_2$ alkyl)(C_1-C_4 alkyl), $-N(C_1-C_4$ alkyl)- $CO-(C_1-C_4$ alkyl), $-NHCO(C_1-C_4$ alkyl), $-COOH$, $-COO(C_1-C_4$ alkyl), $-CONH(C_1-C_4$ alkyl), $CON(C_1-C_4$ alkyl)(C_1-C_2 alkyl), $-SH$, $-CN$, $-NO_2$, $-SO(C_1-C_4$ alkyl), $-SO_2(C_1-C_4$ alkyl), $-SO_2NH(C_1-C_4$ alkyl) and $-SO_2N(C_1-C_4$ alkyl)(C_1-C_2 alkyl);

$-NR^1R^2$ or $-CR^1R^2R^{10}$ may form a 3 to 8 membered ring, that in the case of $-CR^1R^2R^{10}$ is carbocyclic, said ring consisting of single bonds, wherein, when said ring has from 5 to 8 members, one or two of the ring carbon atoms of such a 5 to 8 membered ring may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^3 wherein Z^3 is hydrogen, C_1 - C_4 alkyl, benzyl and C_1 - C_4 alkanoyl, and wherein from one to three of the single bonds of such a 3 to 8 membered ring that are carbon-carbon or carbon-nitrogen single bonds may each optionally be replaced by a double bond;

R^3 is hydrogen, C_1 - C_4 alkyl, $O(C_1-C_4$ alkyl), chloro, fluoro, bromo, iodo, $-CN$, $-S(C_1-C_4$ alkyl) or $-SO_2(C_1-C_4$ alkyl) wherein each of the (C_1 - C_4 alkyl) moieties in the foregoing R^3 groups may optionally be substituted with one substituent R^9 selected from hydroxy, fluoro and (C_1 - C_2

alkoxy);

each of R^4 is, independently hydrogen, (C_1-C_6 alkyl), fluoro, chloro, bromo, iodo, trifluoromethyl, hydroxy, cyano, amino, nitro, $-O(C_1-C_4$ alkyl), $N(C_1-C_4$ alkyl)(C_1-C_2 alkyl), $-S(C_1-C_4$ alkyl), $-SO(C_1-C_4$ alkyl), $-SO_2(C_1-C_4$ alkyl), $-CO(C_1-C_4$ alkyl), $-C(=O)H$ or $C(=O)O(C_1-C_4$ alkyl), wherein one or two of the carbon-carbon single bonds in each of the (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties in the foregoing R^4 groups may optionally be replaced with a carbon-carbon double or triple bond and wherein each of said (C_1-C_6 alkyl) and (C_1-C_4 alkyl) moieties may optionally be substituted with one or two substituents independently selected from hydroxy, amino, C_1-C_3 alkoxy, dimethylamino, methylamino, ethylamino, $-NHC(=O)CH_3$, fluoro, chloro, $-CN$, $-COOH$, $-C(=O)O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl) and NO_2 ;

R^5 is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, furanyl, benzofuranyl, benzothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, benzoxazolyl or C_3-C_8 cycloalkyl wherein one or two of the carbon atoms of said cycloalkyl rings that contain at least 5 ring members may optionally and independently be replaced by an oxygen or sulfur atom or by NZ^4 wherein N^4 is hydrogen, C_1-C_4 is alkyl or benzyl; and wherein each of the foregoing R^5 groups is substituted with from one to four substituents wherein one to three of said substituents may be selected, independently, from chloro, C_1-C_6 alkyl and $-O(C_1-C_6$ alkyl) and one of said substituents may be selected from bromo, iodo, formyl, $-CN$, $-CF_3$, $-NO_2$, $-NH_2$, $-NH(C_1-C_4$ alkyl), $-N(C_1-C_2$ alkyl)(C_1-C_6 alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-C(=O)(C_1-C_4$ alkyl), $-COOH$, $-SO_2NH(C_1-C_4$ alkyl), $-SO_2N(C_1-C_2$ alkyl)(C_1-C_4 alkyl), $-SO_2NH_2$, $NHSO_2(C_1-C_4$ alkyl), $-S(C_1-C_6$ alkyl) and $-SO_2(C_1-C_6$ alkyl), and wherein each of the C_1-C_4 alkyl and C_1-C_6 alkyl, moieties in the foregoing R^5 groups may optionally be substituted with one or two substituents independently selected from fluoro, hydroxy, amino, methylamino, dimethylamino and acetyl;

R^7 is hydrogen, C_1-C_4 alkyl, halo, cyano, hydroxy, $-O(C_1-C_4$ alkyl) $-C(=O)(C_1-C_4$ alkyl), $-C(=O)O(C_1-C_4$ alkyl), $-OCF_3$, $-CF_3$, $-CH_2-OH$, $-CH_2O(C_1-C_4$ alkyl);

R^{10} is hydrogen, hydroxy, methoxy or fluoro;

R^{11} is hydrogen or C_1-C_4 alkyl; and

with the proviso that: (a) when R^4 is attached to nitrogen, it not halo, cyano or nitro; and (b)